

New therapeutic modalities in dermatology

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ABSTRACT

During the past fifteen years there has been a stunning advance in the treatment of many skin diseases, especially those diseases that are chronic and accompanied by many physical and psychological disabilities. An evident example of this is psoriasis, for which a lot of therapeutic methods have been discovered and developed to improve the quality of life of the patients suffering with this chronic disease. Small molecule inhibitors such as Apremilast which is phosphodiesterase-4 inhibitor, seems to be a promising drug for psoriasis with minimal side effects.

Many of these treatments may be outdated or were used to treat conditions other than skin diseases, for example Glycopyrrolate, an anticholinergic drug which is now used to treat hyperhidrosis, but was originally used more than 30 years ago to treat excessive salivation and peptic ulcer.

KEY WORDS: Dermatology, therapeutics, new modalities

INTRODUCTION

During the last decade there have been a lot of changes in diagnostic and therapeutic modalities in dermatology, in both medical and surgical fields. A lot of new concepts have made breakthrough in diagnosing and treating difficult skin diseases, helping patients with skin diseases such as psoriasis to have a better quality of life.

In this article we will discuss some new emerging therapeutic modalities for treating a variety of skin diseases, few of them still under investigation, while others showed some effectiveness and a few failed to improve the target skin disease.

Following are the topics to be discussed in this article :

1. Glycopyrrolate.
2. Topical Timolol.
3. Apremilast.

4. R- Salbutamol.
5. Helium – Neon Laser.
6. Prostaglandin analogues.
7. Tasocitinib.
8. Topical Dapsone 5 % gel.

Glycopyrrolate for Hyperhidrosis

Hyperhidrosis can be generalized or localized, primary or secondary, having a significant psychosocial burden and negative impact on quality of life. The common areas of involvement are palms, soles and axillae, although it can also involve the craniofacial area. The standard treatment can be medical or surgical. Medical options include topical Aluminium chloride at a concentration of 12 to 20%, iontophoresis or injection of botulinum toxin. The surgical options are usually reserved for patients who fail to respond to medical treatments, this include surgical sympa-

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thectomy, surgical excision of the affected areas or subcutaneous liposuction. Each modality has been used effectively.

Anticholinergic drugs block sweat secretion by acting as competitive antagonists of acetylcholine at the muscarinic receptors.¹ Glycopyrrolate is an old anticholinergic drug originally developed for peptic ulcer disease and is used widely for patients with excess saliva drooling. It is a drug in the highly polar quaternary ammonium group and cannot pass through lipid membranes, so it cannot penetrate the brain-nerve barrier, therefore has little effect on the central nervous system.²

In the past few years this old medication has been reevaluated topically and orally for the treatment of primary and secondary hyperhidrosis in both adults and pediatric age groups, in many studies. Topically it is found to be effective in the treatment of various types of localized hyperhidrosis: palmoplantar,³ gustatory hyperhidrosis⁴ and hyperhidrosis in herpetic neuralgia.⁵ Regarding its oral use in many studies, it is proved to be a good modality of treatment for primary hyperhidrosis. In one study, 36 patients were given Glycopyrrolate 1 mg, administered twice a day as the initial dosage. The dosage was increased by 2 mg per day up to a maximum of 8 mg per day, according to the alleviation of symptoms. The results showed that 75% of patients showed an actual decrease in perspiration, and a significant improvement. The main side effects were dry mouth in around 30%, followed by palpitation in 11% and headache in 3% of patients.⁶ In another study on 59 patients with various types of hyperhidrosis, out of which 71% complained of palmoplantar or axillary hyperhidrosis, who were started on Glycopyrrolate 1 to 2 mg once or twice daily, with response seen in 67% (30/45). The fifteen patients

with treatment failures included 6 nonresponders and 9 with adverse effects, including xerostomia and gastrointestinal disturbance.⁷

Even in children, Glycopyrrolate at dose of 2 mg per day was very effective with 90% of patients experiencing improvement and a major response seen in 71% of responders. Improvement occurred within hours of administration and disappeared within a day of discontinuation.⁸ These results have been confirmed in many other studies, but treatment has been limited by side-effects. These side effects included dry mouth, blurred vision, tachycardia, urinary retention and constipation.⁹

Topical Timolol

Recently oral β -blockers such as propranolol has replaced systemic steroids in the treatment of infantile hemangiomas (IH). Timolol is a nonselective β -blocker similar to propranolol, available in a topical gel formulation for treatment of glaucoma. The proposed therapeutic effects of β -blockers e.g propranolol on Infantile Hemangioma are:

1. Vasoconstriction.
2. Decreased expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) genes through down-regulation of the RAF/mitogen-activated protein kinase pathway.
3. Apoptosis of capillary endothelial cells.

Recently topical Timolol has been tried for treatment of small infantile hemangioma.

In one study conducted on 6 children with infantile hemangioma, treated with 0.5% timolol gel for 16 weeks, concluded that timolol maleate, 0.5% gel was effective and safe for the treatment of IHs, with similar efficacy also reported in many other studies and case reports later on.^{10,11} In a recent large retrospective cohort study on 73

patients from five centers (2 in Canada, 2 in the US, and 1 in Australia), demonstrated efficacy of topical timolol and gradual improvement with longer treatment. The mean improvement at the last follow-up visit was $45 \pm 29.5\%$. Longer treatment duration was associated with greater improvement in IH appearance.¹² (Fig. 1)

The topical timolol 0.5% ophthalmic solution was effective in most cases with small superficial IHs, while it lacks this effectiveness in the deep IHs and the children had to be treated during the whole proliferative phase.¹³ Topical timolol is available in two forms 0.5% solution or 0.1% gel, although some studies have used 0.5% gel. Both of them are effective but the hydrogel formulation has less side effects especially cardiovascular side effects which are minimal if the topical timolol is used for small IHs.^{14,15} Although Timolol is absorbed in

relatively small amounts from topical use, some patients remain exposed to potentially life-threatening cardiac depression and bronchospasm. Other side effects reported include neuropsychiatric disturbances eg. fatigue, confusion, depression, exacerbation of peripheral vascular disease and disturbance of serum lipoproteins, similar to those seen with oral β - blockers.¹⁶

Apremilast

Apremilast belonging to the class of small molecule inhibitors, is an orally administered phosphodiesterase-4 inhibitor (PDE) which is currently in phase 2 clinical studies for psoriasis and other chronic inflammatory diseases.¹⁷ This new treatment modality has several selective phosphodiesterase-4 inhibitors including cilomilast and roflumilast.¹⁸ Psoriasis is considered to be a Th1 autoimmune skin disease in which there is involvement of pro-inflammatory cytokines such as interferon (IFN)- γ and tumour necrosis factor (TNF)- α .¹⁹

Cyclic nucleotide PDEs are a family of enzymes that catalyze the degradation of cAMP and cyclic guanosine -3, 5- monophosphate (cGMP) to their corresponding 5- nucleotide monophosphates, leading to inactivation of cAMP and cGMP (Fig. 2). Eleven PDE families have been identified till now, and of these PDE4 is probably the most extensively studied.²⁰

Many studies demonstrate the broad anti-inflammatory effects of apremilast in vitro, namely the inhibition of production of multiple mediators including TNF- α , IFN- γ , CXCL9, IL-2, IL-12, IL-23, macrophage inflammatory protein (MIP)-1a, monocyte chemoattractant protein (MCP)-1 and granulocyte macrophage-colony stimulating factor (GM-CSF) from peripheral blood mono-



Fig. 1 Response of hemangioma to timolol maleate 0.5% gel-forming solution over 6 months. (photograph courtesy of Dr. Ajith Chakkittakandiyil).

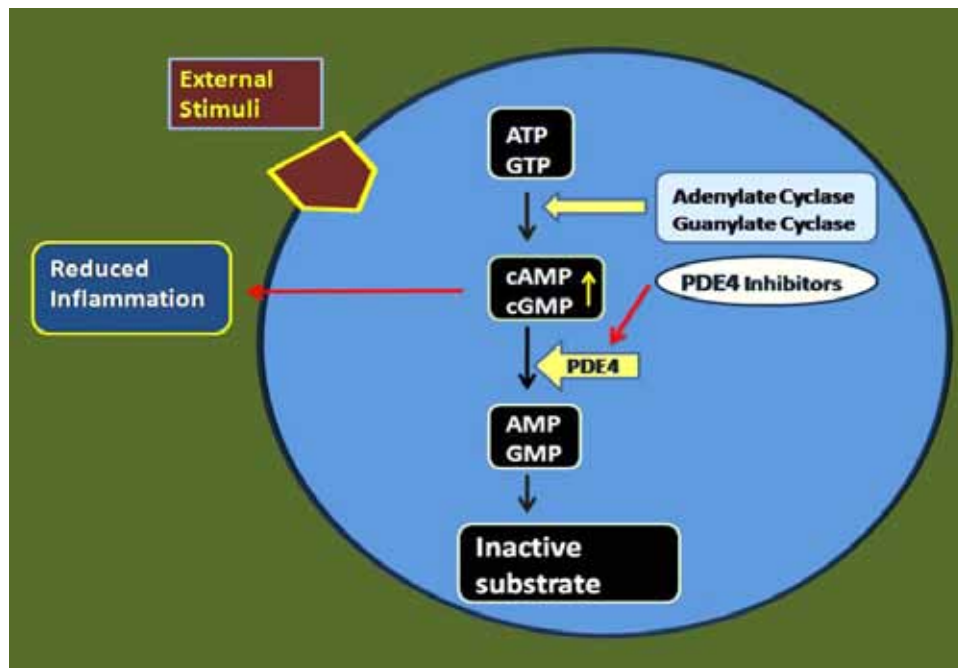


Fig. 2 Action of PDEs. In response to external stimuli, ATP and GTP are phosphorylated to cAMP and cGMP by adenylate and guanylate cyclases. PDEs inactivate cAMP and gAMP. Inhibition of PDEs results in an increase in intracellular cAMP and cGMP, which reduce inflammation.

nuclear cell (PBMC). The responses of polymorphonuclear cells (PMN), including IL-8 and LTB₄ production were also inhibited by apremilast.²¹ In histopathology apremilast causes statistically significant reductions in epidermal thickness and proliferation index, compared with the vehicle-treated groups.²²

Apremilast has been investigated in several studies for psoriasis. In a randomized, double-blind, placebo (PBO)-controlled study on 352 patients with moderate to severe plaque psoriasis (PASI >12; BSA >10%), both Apremilast 20 mg BID and 30 mg BID doses were efficacious in reducing the severity of moderate to severe plaque psoriasis. Apremilast 30 mg BID showed an incremental increase of response without significant safety signals and with an acceptable tolerability profile. Therefore, 30 mg BID has a better overall risk-benefit profile.²³ Apremilast also showed good response in 15 patients with cutaneous sarcoidosis, with a significant reduction in the induration. Al-

though some patients developed significant worsening of their cutaneous lesions, but generally apremilast was effective in treating cutaneous sarcoidosis.²⁴ Recently it has been tried in treatment of atopic dermatitis in 16 patients. Apremilast 20 mg twice daily, displayed a significant reduction in pruritus from baaseline and those on a dose of 30 mg twice daily, displayed a significant reduction of (Eczema Area and Severity Index) EASI in 3 months.²⁵

R-salbutamol

R-salbutamol is a β_2 -receptor agonist, which inhibits the activity of CD4⁺ T lymphocytes and other cells with a high density of β_2 receptors such as monocytes, macrophages and Langerhans cells. Binding of the β_2 -receptor agonist to these cells inhibits proliferation and secretion of proinflammatory products e.g IL-2 and IFN- γ in human T cells. Furthermore, R-salbutamol inhibits superoxide generation and peroxidase release



Fig. 3 The effect of topical R- Salbutamol on (SCLE) before and 2 - 4 weeks (photograph courtesy of Dr. Hans Christian Wulf).

from stimulated human granulocytes. These effects might have therapeutic potential in cutaneous lupus.

Recently, R-salbutamol has been formulated as an oil-in-water emulsion suitable for topical administration. R-salbutamol 0.5% cream was found to be very effective in a study on 4 patients with subacute lupus erythematosus (Fig. 3) as well as in 3 patients with discoid lupus (DLE), but patients with hypertrophic type were found to be resistant to it.²⁶ A multicentre, double-blinded, randomized, placebo-controlled phase II trial of 37 patients, concluded that application of R-salbutamol cream 0.5% was safe and well tolerated.

They observed statistically significant effects on scaling/hypertrophy, induration, pain and itching as well as patient global assessment, suggesting that R-salbutamol could be a promising new topical therapeutic alternative for DLE.²⁷ Side effects of topical R-salbutamol are minimal mostly in the form of toxic eczema which respond well to topical steroid.

Helium - Neon Laser

Low-energy helium - neon lasers (632.8 nm) have been employed in a variety of clinical treatments including vitiligo management. Light-mediated reaction to low energy laser irradiation is referred

to as biostimulation rather than a thermal effect. Recently this type of laser has been tested to treat segmental type of vitiligo (SV). Segmental vitiligo (SV) is a special form of vitiligo occurring in a dermatomal distribution and involving an abnormality in the sympathetic nerves supplying the affected dermatome.²⁸ Recently it has been shown that SV is associated with an abnormal increase in cutaneous blood flow and adrenoceptor responses in the affected areas.

Mechanism of action of He – Ne Laser in segmental vitiligo:

1. Significant increase in basic fibroblast growth factor (bFGF) release from both keratinocytes and fibroblasts and a significant increase in nerve growth factor (NGF) release from keratinocytes.

Which leads to proliferation of cultured melanocytes & enhance the migration & survival of melanocytes.

2. He-Ne laser normalizes the dysfunctions of cutaneous blood flow and adrenoceptor re-

sponses in SV patients.

Cutaneous blood flow was significantly higher at SV lesions compared with contralateral skin, but this was normalized after He-Ne laser treatment.²⁹ Thirty patients with segmental-type vitiligo on the head and/or neck were enrolled in a study and Helium-Neon laser light was administered locally at 3.0 J per cm² with point stimulation once or twice weekly. After an average of 16 treatment sessions, initial repigmentation was noticed . Marked repigmentation (> 50%) was observed in 60% of patients with successive treatments (Fig. 4).^{30,31}

Actually He-Ne laser is an old laser which was used to improve wound healing process. Most of the studies that have been done on He-Ne laser use for segmental vitiligo were from single center in Taiwan. These results, which were excellent in these studies need more larger and controlled confirmatory studies.

Prostaglandin analogues

Latanoprost is a prostaglandin F2- α (PGF₂ α) analogue and bimatoprost also has a similar method

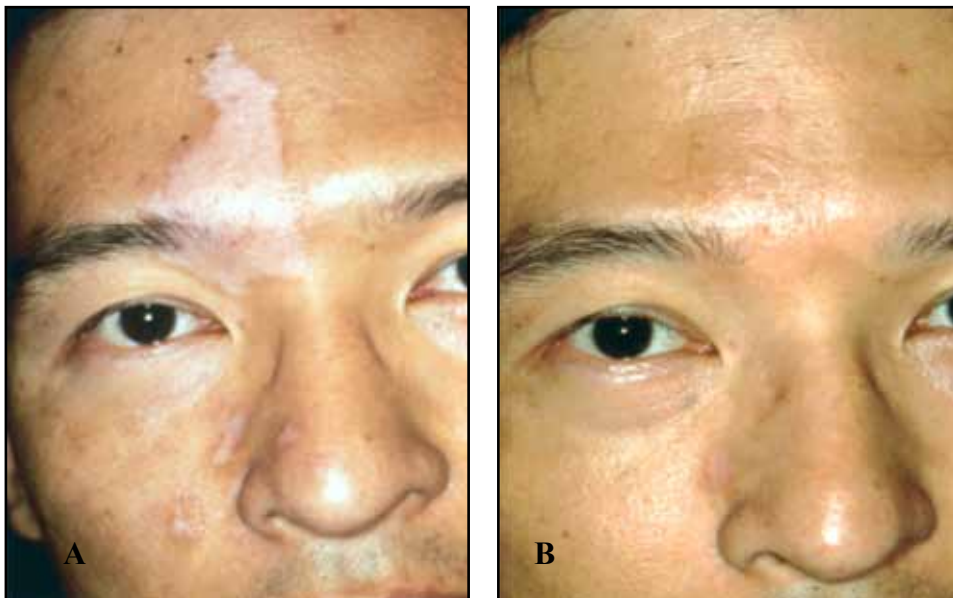


Fig. 4 A 39-y-old man had vitiligo on right forehead and paranasal area for 1.5 y. And to left after 142 sessions of He-Ne laser irradiation, 90% repigmentation was observed. (photograph courtesy of Dr. Hsin-SuYu).

of action. Prostaglandin and prostamide analogs may also prolong the anagen phase of eyelashes, leading to an increase of eyelash length.³² These medications have been observed to cause eyelash hypertrichosis,³³ leading to many studies being conducted to test the effects of these medications in the treatment of alopecia areata of the eye lashes.

Bimatoprost ophthalmic solution once daily was well tolerated but not effective in promoting eyelash growth in patients with 95% or greater eyelash loss caused by AA, although patients with less extensive eyelash loss caused by AA may benefit from treatment with instilled bimatoprost.³⁴ In other studies Bimatoprost 0.03% was found to be effective at enhancing eyelashes growth in adults in the absence of eyelashes AA with a very good safety profile^{38, 39, 40} (Fig. 5). Topical latanoprost has shown no efficacy in the treatment of eyelashes alopecia areata^{35,36} although some studies have shown that Latanoprost may be an effective drug in the treatment of eyelash AA with acceptable responses (total to moderate) in 45% of the patients.³⁷



Baseline (GEA score 1)



Week 16 (GEA score 4)

Fig. 5 The effects of Bimatoprost 0.03% on eyelashes growth. (photograph courtesy of Dr. Stacy Smith).

Tasocitinib

Tasocitinib is another small molecule inhibitor and an orally active immunosuppressant. This new medication is being developed for the treatment of rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, psoriasis, psoriatic arthritis, and for the prevention of transplant rejection. Tasocitinib specifically inhibits Janus activated kinase 3 (JAK3), which has a pivotal role in cytokine signal transduction that governs lymphocyte survival, proliferation, differentiation and apoptosis.⁴¹ Tasocitinib orally, significantly improves the symptoms of moderate to severe psoriasis with early onset of efficacy.

In a 12-week, double-blind, placebo-controlled study, adult patients (n = 197) with psoriasis affecting >15% body surface area (BSA) and a Psoriasis Area and Severity Index (PASI) score >13, were randomized to receive oral tasocitinib (2, 5, or 15 mg BID) or placebo for 12 weeks. Efficacy measures assessed during treatment included PASI and Physician's Global Assessment (PGA). There were significant responses as compared to placebo in patients treated with tasocitinib within 2 weeks and dose-dependent responses continued to increase over time. At week 12, the PASI 75 responses for tasocitinib 2, 5, and 15 mg BID were 25%, 40.8%, and 67 % respectively, versus 2% of the placebo. Tasocitinib was generally well tolerated in the study with the most frequent adverse events being upper respiratory tract infections and headache.⁴²

Occasional adverse events associated with tasocitinib are: Anaemia, diarrhea, headache, lipid metabolism disorders, nasopharyngitis, nausea, neutropenia, respiratory tract infections, sinusitis, urinary tract infections, and rarely abdominal pain, acne, diverticulitis, elevated aminotransfer-

ase levels, herpes zoster, infections, pneumonia, renal failure, staphylococcal infections, tuberculosis.⁴³ In patients with psoriasis also, tasocitinib produces significant and rapid reduction in pruritus, with severity continuing to diminish over 12 weeks of treatment. This reduction in pruritus observed with tasocitinib is clinically meaningful for the vast majority of patients.⁴⁴

Dapsone 5% gel

Dapsone or sulfone is anti-inflammatory and antimicrobial drug that is used mainly to treat leprosy, dermatitis herpetiformis and many other dermatological diseases. This drug was effectively used orally before the era of Isotretinoin to treat acne vulgaris, but was limited by its potential systemic side effects. Recently dapsone has been formulated in an aqueous 5% gel that allows clinically-effective doses of dapsone to be administered topically with minimal systemic absorption. The mechanism of action of topical dapsone gel in treating acne is not known, but it may be related to its anti-inflammatory and antimicrobial properties.

In the last few years a lot of clinical studies have been conducted on topical dapsone 5% gel being used for treatment of acne vulgaris. In a large study (N=3010), patients aged 12 years of age and older with acne vulgaris participated in two identically designed 12-week, randomized, double-blind treatment with twice-daily monotherapy with dapsone gel, 5% versus a vehicle gel. Dapsone gel -treated patients achieved superior results in terms of the investigator's global acne assessment, mean percentage reduction in inflammatory, non-inflammatory and total lesion counts at week 12. Although Clinical improvement was observed with both inflammatory and non-inflammatory

lesions, dapsone gel was particularly effective for inflammatory acne lesions with reductions in inflammatory lesions being apparent as early as 2 weeks and reaching statistical significance by 4 weeks. No clinically significant changes were observed in laboratory parameters, including hemoglobin, even among glucose-6-phosphate dehydrogenase-deficient patients. Adverse events were comparable between the treatment groups and rarely led to discontinuation.⁴⁵ Similar results have been reported in many other studies.^{46, 47, 48}

The side effects that have been seen in many studies were minimal and include: erythema, oiliness/peeling, dryness, nasopharyngitis, upper respiratory tract infection and headache.⁴⁹ The serious hematological side effects and hemolysis that are frequently seen with use of oral dapsone have been investigated with topical dapsone gel, even in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. After treatment with dapsone gel 5%, no clinical or laboratory evidence of drug-induced hemolytic anemia was noted, even in G6PD-deficient subjects with acne vulgaris.⁵⁰

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